REMARKS/ARGUMENTS

Claims 1, 8, 9, 18, and 23-30 are active in this application.

Support for the amendment to Claim 1 and Claim 26 is found on pages 7-13. Claims 27-30 are supported by original Claims 18, 20, 21, and 23.

No new matter is believed to have been added by these amendments.

Upon entry of the amended claims, the following rejections are no longer applicable and as such it is requested that they be withdrawn: (1) Claim 7 under 35 USC 101 in view of US 6,869,954; (2) Claims 10-12 under 35 USC 101 in view of US 6,861,428, (3) Claims 4-6 under 35 USC 101 in view of US application serial no. 10/960,993; and (4) Claim 22 under 35 USC 101.

The rejection of claim 23 under 35 USC 112, first paragraph is respectfully traversed.

As discussed in the application on pages 1-2, rheumatism, arthritis, osteoporosis, inflammatory colitis, immune deficiency syndrome, ichorrhemia, hepatitis, nephritis, ischemic diseases, insulin-dependent diabetes mellitus, arterial sclerosis, Parkinson's disease, Alzheimer's disease, and leukemia, an increased production of interleukin-1β, which is an inflammatory cytokine, is observed. This interleukin-1β serves to induce synthesis of an enzyme which is considered to take part in inflammation-like collagenase and PLA2--and, when intra-articularly injected to animals, causes multiarticular damage highly resembling rheumatoid arthritis. In a healthy body, on the other hand, the activity of interleukin-1β is controlled by interleukin-1 receptor, soluble interleukin-1 receptor and interleukin-1 receptor antagonist.

The present inventors previously reported in WO 99/44995 that high inhibitory activity against interleukin-1.β production was observed on phenylpyridazine derivatives. Recently, certain phenylpyridazine derivatives having inhibitory activity against interleukin-1β production have been reported (JP 7-69894 A, WO 98/41511, WO 99/10331, WO 99/10332, WO99/25697, WO00/50408). These reported compounds, however, are different in chemical structure from the compounds of the present invention.

The compounds disclosed in WO 99/44995 exhibit strong inhibitory activity against interleukin-1β production. However, the water solubility of these compounds is so low that formulating them into pharmaceutical preparations, such as tablets, required further investigations. In the course of a further investigation, the present inventors discovered that the introduction of a substituted or unsubstituted aminoalkyl group to the 4-position of 6-phenylpyridazin-3-one affords a compound useful as a preventive or therapeutic for immune system diseases, inflammatory diseases, and ischemic diseases, for example, due to its significantly improved water solubility, good oral absorbability and excellent inhibitory activity against interleukin-1βproduction, leading to the completion of the present invention.

The unique phenylpyridazine derivative represented by the formula (1) exhibit both this strong IL-1β inhibitory activity and water-solubility. In fact, the specification provides data of a representative number of compounds falling within the definition of the claims that exhibit this strong IL-1β inhibitory activity (see pags 309-311 of the specification).

Given that IL-1β is known in the field to be involved in a wide-range of diseases, it is submitted that one can certainly practice the invention claimed in Claim 23 without undue experimentation. If the disease has an IL-1β component, then the

compounds of the invention can be administered to treat the disease. As for dosages, administration schedules, this is well-known to vary from individual to individual and will depend on any number of factors including race, age, sex, severity of condition, etc. It is common and, in fact, routine in the pharmaceutical arts to modify treatment regimens according to the specific needs of a patient. Therefore, this certainly cannot be considered undue experimentation.

As evidence of what the field knows about IL-1β and its involvement in the pathologies of several diseases, Applicants attach hereto 9 publications. Each is briefly discussed below.

Rossenwasser (*J Allergy Clin Immunol*, 102(3) Sept. 1998) generally explains that IL-1 is involved in the onset of such diseases as immune system disease, arthralgias, septic shock and colitis in view of its relation with inflammation (left column, page 345, also Table II and Ill.)

Chang et al (Am J Respir Crit Care Med, vol. 156, 1230-1234 (1997) explains the correlation between IL-1β and ischemic diseases. Briefly, IL-1βsecreted during ischemic state stimulates the deposition of leucocytes at the inflammatory cite, by which endothelial cells and intercellular matrix are damaged due to activated oxygen etc. secreted from the localized leucocytes.

Assuma et al (J Immunol, 160:403-409 (1998) and Romas et al (Osteopros Int (1997), 7 (Suppl. 3):S47-S53) explain the correlation between IL-i and osteoporosis. Assuma et al specifically describes the correlation of IL-1β and tooth loss in view of periodontal inflammation, and explains that the mechanism by which tooth loss is induced is attributable to excess host response (i.e., local inflammatory reaction, enhanced osteoclastic activity by IL-1β rather than direct bacterial infection (see page 408, lower right corner) and further states in the last 4 sentences of the Assuma et al

that although osteoporosis has a different etiology than bone loss by tooth loss, both tolerate through a common mechanism involving IL-I. Romas et al explains that IL-1β enhances osteoclast-mediated resorption, by which the balance of bone resorption and formation is disrupted and the chance of developing osteoporosis increases.

Wilson et al (J. Antimicrobial Chemotherapy 41, Suppl. A: 51-63 (1998)) explains the correlating between IL-I and Ichorrhemia (sepsis), more specifically, septic shock induces a systemic inflammatory response (see the section Systemic inflammatory response syndrome, especially lines 5-7 in right column in page 52.)

Chernow (Chest 112(6) (1997)) further teaches that blockage of IL-i is effective for easing the inflammatory response caused by septic shock. (Lines 5-8, right column in page 321S.)

Li et al (Cell 80:401-411 (1995) presents experimental data (i.e., Fig. 5) illustrating higher survival rate of ICE-deficient mice which produce non-detectable amount of IL-1β after being subjected to LPS-induced septic shock. The article summarizes the ffect of inhibition of IL-1β production on septic shock and further mentions the therapeutic possibility for rheumatoid arthritis. (See from the last 4 lines of page 407 to the end of the paragraph.)

Mollina et al (J Clin Invest 84:733-737 (1989) explains that the fever and the wasting syndrome seen in AIDS patients may be caused by overproduction of IL-1β, and further, excess of IL-1β may activate T-cells, which increase the patient's susceptibility to HIV infection.

Arend et al (Arthritis and Rheumatism, 38(2):151-160 (1995)) illustrates effects of inhibition of IL-1β in rheumatoid arthritis. IL-1β is known to be a kind of inflammatory cytokines, and is known to be a causative factor for arthritis. This article specifically talks about the correlation between IL-1β and rheumatism.

In view of the above, Applicants request withdrawal of the rejection of Claim 23 under 35 USC 112, first paragraph.

The rejection of Claim 23 under 35 USC 112, second paragraph is also respectfully traversed.

The essential inquiry pertaining to the requirement under 35 U.S.C. § 112, second paragraph is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See MPEP § 2173.02

As discussed above, what constitutes a disease having an IL-1β component can be readily ascertained. In fact, the art recognizes multiple diseases in which this interleukin is a major component. As for dosages, administration schedules, and the effective dosages this is well-known to vary from individual to individual and will depend on any number of factors including race, age, sex, severity of condition, etc. It is common and, in fact, routine in the pharmaceutical arts to modify treatment regimens according to the specific needs of a patient. This causes no concern. One of skill in the art can easily ascertain whether the a disease has an IL-1β component or not. Whether certain diseases may not be suitably treated is not the relevant inquiry as claims are permitted to encompass both operative and inoperative embodiments.

Applicants request withdrawal of this rejection.

The rejections of Claims 1-23 under the doctrine of obviousness-type double patenting in view of US 6,869,954; 6,861,428; and application no 10/960,993 (now US 7,087,606) are addressed by the Terminal Disclaimer filed herewith.

A Notice of Allowance for all pending claims is earnestly solicited.

Should the Examiner deem that any further action is necessary to place this application in even better form for allowance, he is encouraged to contact Applicants' undersigned representative.

Respectfully submitted,

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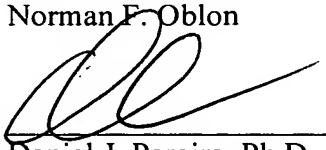

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